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The brain-gut axis in irritable bowel syndrome – clinical aspects

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Summary

Irritable bowel syndrome (IBS) is the most common chronic gastrointestinal (GI) disorder, affecting about 20% of the world's population. Chronic abdominal pain or discomfort relieved by defecation and associated with altered bowel habits are the mainstay in diagnosis. The pathophysiology of IBS remains unknown. This biopsychosocial disorder involves dysregulation of the nervous system, altered intestinal motility, and increased visceral sensitivity. All of these result from dysregulation of the bidirectional communication between the gut with its enteric nervous system and the brain (the brain-gut axis), modulated by various psychosocial and environmental factors (e.g. infection, inflammation). Numerous neurotransmitters are found in the brain and gut that regulate GI activities, including 5-hydroxytryptamine (5-HT, serotonin) and its 5-HT_3 and 5-HT_4 receptors. The current approach to IBS patients is based on a positive diagnosis of the symptom complex, exclusion of underlying organic disease, and institution of a therapeutic trial. Traditional symptomatic treatment has included antidiarrheals, laxatives and bulking agents/fiber, low-dose tricyclic antidepressants, antispasmodics for pain, and 'alternative' therapies (e.g. psychotherapy, hypnotherapy). The scientific evidence supporting this therapy is limited. Novel approaches include visceral analgesics and serotonin agonists and antagonists. In patients with severe diarrhea, 5-HT_3 receptor antagonists (e.g. alosetron) and selective M_3-type anticholinergics are indicated, in constipation 5-HT_4 agonists (e.g. tegaserod), and in pain alfa$_2$-adrenergics (e.g. clonidine), cholecystokinin antagonists, kappa-opioid agonists (e.g. fedotozine), and neurokinin antagonists; some of these agents are still being investigated. Understanding the brain-gut axis is crucial in the development of effective therapies for IBS.

key words: **brain-gut axis • irritable bowel syndrome • pathophysiology • serotonin • treatment**

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BACKGROUND

Irritable bowel syndrome (IBS) is a chronic disorder of the gastrointestinal (GI) function characterized by continuous or remittent abdominal pain and is associated with altered bowel habits, diarrhea or constipation or both, and bloating [1]. The disorder cannot be explained by specific pathophysiologic mechanisms, or structural or known biochemical abnormalities. IBS symptoms are multi-determined and are generated from dysregulation at multiple levels of the brain-gut axis (BGA). They are manifested by abdominal motor reactivity to various stimuli and low sensation and pain thresholds. Psychosocial factors also have an important role in modulating both the disease experience and clinical outcome. IBS is highly prevalent and can be associated with significant emotional distress, impaired health-related quality of life, disability, and high health care costs [2,3].

IBS is one of the most common clinical problems encountered by the general practitioners and gastroenterologists [4,5]. Approximately 10–15% of the general population has IBS, and more than 40% of IBS patients have such frequent and severe symptoms as to lead to a reduction in quality of life and result in numerous visits to physicians. The economic impact of IBS is large [5]. The estimated health care costs of IBS in the United States are very high, with $19.2 billion annual indirect costs (e.g. work absenteeism, reduced productivity) and $1.6 billion direct medical expenses (e.g. visits to healthcare providers, diagnostic workups, treatment) [2,5,6].

There are no specific laboratory tests or physical markers that are pathognomonic for IBS. Therefore the diagnosis is based on symptoms and clinical features as well as an absence of any alarm indicators [3,7,8]. In 1978, Manning and associates established six criteria to distinguish IBS from organic bowel disease. Talley and co-workers showed that the Manning criteria are sensitive in 58% and specific in 74% of cases in discriminating IBS from organic GI diseases [9,10]. These criteria were updated in 1999, and the Rome criteria have come to be accepted as the state-of-the-art criteria for research studies and clinical practice [3]. According to the Rome criteria, IBS is defined on the basis of abdominal pain and alteration of bowel habits. The symptoms are used to differentiate three subgroups of patients: those with constipation-predominant IBS, those with diarrhea-predominant, and those with alternating bowel movements [11]. The Rome criteria have a positive predictive value of approximately 98% and additional diagnostic tests have a yield of 2% or less [7]. However, many authors suggest that the diagnostic criteria for IBS need further validation [10,12].

IBS is heterogeneous in nature, and patients experience not only abdominal discomfort and bowel problems, but sometimes many other symptoms, including heartburn, back pain, headache, urinary frequency, muscle pains, menorrhagia, dyspareunia, anxiety, and depression [1]. It is essential to differentiate between organic and functional causes of symptoms. An organic pathology may be suspected in a patient with any of the so-called alarm features: beginning of symptoms at an age over 50 years, progression or worsening of symptoms without periods of relief, nighttime symptoms, rectal bleeding, anemia, hypoalbuminemia, anorexia, unexplained weight loss, recurrent vomiting, family history of colon cancer, abnormal physical findings (e.g. mass), and extraintestinal manifestations as seen in inflammatory bowel disease [8]. The presence of any of these features is usually an indication for further investigations (Table 1) [10].

EPIDEMIOLOGY

Epidemiologic studies are difficult to interpret because there is a lack of clear pathologic features of IBS [1]. The investigated population may vary according to the nature and interpretation of the diagnostic criteria. IBS seems to be as common in American and Asian as it is in European countries. Prevalence seems to be similar in whites, blacks, and Hispanics [2]. The overall prevalence from questionnaire studies is 2.9%, but population-based studies in the USA estimate the prevalence of IBS between 5% and 25% [2,3,5]. The precise incidence of IBS is unclear, but it has been estimated at 1–2% per year [5]. Although the majority of people with IBS do not consult a physician, approximately 10–25% of patients seek family practice and 1% is referred to a gastroenterologist [6,14]. The prevalence of IBS is 3–4 times greater in women than men, and female patients seem to have more frequent and severe symptoms and they seek health care more often [1–3].

IBS can affect people at any age, but the prevalence of IBS declines with age [15]. Approximately 50% of people with IBS report beginning of symptoms before the age of 35 [3]. Traditionally, IBS is not diagnosed in people after the age of 60, when organic diseases of the gut become more frequent [1,3,5,15].

IBS does not increase mortality or the risk of inflammatory bowel disease or cancer. Patients with IBS who seek medical attention are more disturbed psychologically, more likely to have abnormal personality profiles, are more concerned about their health and fearful of illness [5].

PATHOPHYSIOLOGY

The pathophysiology of IBS is heterogeneous and not fully elucidated. Recent studies have led to a greater understanding of the association between the gut and CNS. Currently, the model for IBS incorporates enhanced motility, abnormal sensation, and autonomic reactivity modulated by CNS-enteric nervous system (ENS) interaction, or the BGA. Moreover, enteric infection, immune activation, and inflammation of the colonic mucosa as well as the enteric neuro-muscular apparatus play a role in the pathophysiology of IBS [4,16].

IBS is recognized as a biopsychosocial disease in which several major mechanisms interact, including enhanced visceral sensation (visceral hypersensation), central perception of visceral events, abnormal intestinal motility, and abnormal psychosocial factors [3,4].

Table 1. The Manning and Rome II diagnostic criteria for irritable bowel syndrome [13,14].

Manning criteria	Rome II criteria
Onset of pain associated with more frequent bowel movements Onset of pain associated with looser bowel movements Pain relieved by defecation Visible abdominal distention Subjective sensation of incomplete rectal evacuation (more than 25% of the time) Passage of mucus (mucorrhea; more than 25% of the time)	At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has 2 of 3 features: 1. Relieved with defecation; and/or 2. Onset associated with a change in frequency of stool; and/or 3. Onset associated with a change in form (appearance) of stool Symptoms that cumulatively support the diagnosis of IBS: 1. Abnormal stool frequency (greater than 3 bowel movements per day or less than 3 bowel movements per week) 2. Abnormal stool form (lumpy/hard or loose/watery) 3. Abnormal stool passage (straining, urgency or feeling of incomplete rectal evacuation) 4. Passage of mucus 5. Bloating or feeling of abdominal distention

Dysregulation of the Nervous System

The GI tract is innervated by five different classes of neurons: intrinsic enteric, vagal afferent, spinal afferent, parasympathetic efferent, and sympathetic efferent [17]. Each aspect of digestive activity is under the regulatory influence of neurons, among which the ENS plays the most important role [17,18].

The ENS, also called the 'little brain' of the gut, functions independently of the CNS [17,19]. It controls GI motility and secretion and is involved in visceral sensation. The ENS has been shown to exert an important role in the regulation of several intestinal mucosal functions, including mucosal blood flow, regulation of epithelial permeability, organization and cell proliferation (20). All of these functions contribute to the maintenance of the intestinal barrier [20].

Brain-gut bidirectional communication plays a prominent role in the modulation of gut function. Signals from sensory sources (e.g. sound, sight, smell, somatic and visceral sensations) to the brain play a role in reflex regulation and in the modulation of mood states [2]. These inputs are modified by memory, cognition and affect, then integrated within neural circuits in the CNS, spinal cord, autonomic nervous system (ANS), and ENS [2,3,18]. These inputs can have physiologic effects, such as changes in motility, secretion, immune function, and blood flow within the GI tract [2,3]. The emotional motor system in the brain is a revised name for the limbic system, and some paralimbic structures (including the medial prefrontal cortex, amygdale, and hypothalamus) communicate emotional changes via the ANS to the gut [2]. The CNS is also essential in the perception of events occurring within the gut. Alteration at any level can lead to altered sensation, dysmotility, or psychological distress. In IBS, dysregulation has two components. There may be dysregulation of motor nerves regulating GI smooth muscle contraction, resulting in abnormal intestinal motility, or there may be dysregulation of the sensory nerves linking intestinal receptors and nerve endings to the CNS, resulting in enhanced awareness and hypersensitivity to abdominal distension, contraction, and discomfort [2].

The activation of the modulatory systems is dependent on peripheral and central events. Stress, anxiety, or recall of some memories can enhance the perception of painful events, whereas distraction, hypnosis, and relaxation can decrease perceptual sensitivity [2]. Stress-induced visceral hyperalgesia may be an important mediator of visceral hypersensitivity in IBS patients [2].

Imaging studies of regional central blood flow during rectal distention give us evidence of the importance of altered brain perception of visceral stimuli [8,16]. Using distal colonic stimulation in IBS patients, a greater activation of the midcingulate cortex, a brain region concerned with attentional processes and response selection, was shown. This region, modulated by hypnotic suggestion, was associated with changes in the subjective unpleasantness of a somatic pain stimulus in another study [2]. Hypnosis is likely to modulate attentional mechanisms (including the midcingulate cortex), and relaxation exercises involving deep breathing techniques may alter vagal afferent input to the brain [2]. Centrally targeted medications, such as anxiolytics, low dose tricyclic antidepressants, and corticotropin releasing factor 1R (CRF-1R) antagonists, all involve inhibitory effects on the responsiveness of the emotional motor system and provide options for future therapeutic investigations [2].

Abnormal Intestinal Motility

About 25–75% of patients with IBS have disturbances in GI motility [2]. Many studies identified abnormal patterns of contractile activity and electrical activity in the colon of patients with IBS. Patients with diarrhea-predominant IBS have a greater number of fast colonic contractions and propagate contractions with subsequent accelerated transit [3]. Patients with constipation-predominant IBS have a decreased number of fast colonic and propagated contractions, and fewer high-amplitude propagated contractions with slowed whole-gut transit [3]. Patients with abdominal pain have significantly more 'cluster' contractions, which are groups of brief propagated intestinal contractions of higher amplitude than in healthy controls [21].

Motility abnormalities may interact with low sensory thresholds to produce symptoms: delayed transit of gas causes greater abdominal perception in IBS, and IBS patients are more likely than healthy controls to perceive the occurrence of normal migrating motor complexes [2].

The factors controlling GI function may be exacerbated by environmental factors such as stress, provocative stimuli including cholecystokinin, neostigmine, corticotropin-releasing hormone, and intestinal factors such as the presence of food in the gut or bile acids [1].Irregular spontaneous contractions may result in distension of the gut.

Hyperactivity of the enteric nerves in patients with IBS may play a role in disturbance of GI motility [3]. Several neurotransmitters are involved in the regulation of motility and pain in the gut, including 5-hydroxytryptamine (5-HT; serotonin) [18].

Visceral Hypersensitivity

It was first reported by Ritchie in 1973 that IBS patients have pain at lower volumes and pressures when a balloon is inflated in the bowel [2]. Other authors showed that the threshold of reporting pain is below the normal range in 50–70% of IBS patients [2]. The patients are more sensitive to normal intestinal activity and distensions of the colon [1]. Diarrhea-predominant IBS patients exhibit lower thresholds for sensation of gas, stool, and discomfort in the distal colon, and urgency is developed at lower volumes of rectal balloon distention [3]. Patients with constipation-predominant IBS develop discomfort at greater distention volumes than healthy controls [3].

The enhanced pain sensitivity in IBS patients is related to increased visceral sensitivity. Visceral hypersensitivity is recognized by many investigators as a biological marker for IBS [2–4]. The mechanisms of visceral hypersensitivity include increased end-organ sensitivity with recruitment of silent nociceptors, spinal hyperexcitability with activation of nitric oxide and other neurotransmitters via endogenous modulation of caudal nociceptive transmission, and development of long-term hyperalgesia due to the development of neuroplasticity (permanent or semipermanent changes in neural response to chronic or recurrent visceral stimulation) [3].

Changes in Sensory Activity

The CNS responds to impulses from all parts of the body by initiating appropriate biochemical and biophysical actions in target organs and tissues [3]. In patients with IBS, some of the CNS pathways may be hyperactive and inappropriately exaggerate the sensation of abdominal activity and pain [3]. This is probably caused by an increase in the number of nociceptors in the abdomen, overactive nociceptor nerves in the spinal cord following repeated distention of the colon, and psychological factors [3].

Psychosocial Factors

Psychological and psychiatric problems such as somatization, anxiety, hypochondriasis, depression, and phobia are common in patients with IBS [3,4]. Psychological stress and anxiety may exacerbate GI symptoms in normal as well as in IBS patients [3]. It is well known that IBS reduces quality of life, which may have psychological consequences [3]. About 50% of patients with IBS have these problems at the time of diagnosis [3]. Psychological and sociocultural factors in patients with IBS influence not only the illness experience, but also the treatment outcome. Psychosocial factors include: a history of emotional, sexual, or physical abuse, stressful life events, chronic social stress, or anxiety disorder, and maladaptive coping style. Some of these psychosocial influences may occur early in life [2].

Postinfectious IBS

The relationship between enteric infection and alteration in gut immune function as well as the subsequent development of IBS is well documented [1,2,21,22]. A group of IBS patients develops the IBS symptoms with the onset of gastroenteritis (so-called postinfectious IBS; PI-IBS). In prospective studies, IBS symptoms were found in 20–30% of patients who had recovered from a bacterial gastroenteritis [2]. There are several risk factors of PI-IBS, including: female gender, severe and long acute gastroenteritis, and the presence of significant psychological disturbances occurring around the time of the infection [1,2,4,23]. It is believed that gastroenteritis may sensitize the bowel, but the development of IBS depends on the coexistence of psychosocial factors [1].

Many studies have shown that patients with PI-IBS have a variety of functional and morphological alterations, including changes in gut motility, epithelial function, increase in colonic enterochromaffin cells, lymphocytes, mast cells, increased cellularity of lamina propria, lymphocytic infiltrates of the myenteric plexus, and increased nitric oxide synthetase in colonic mucosa [2,4,22]. In addition, patients with PI-IBS were found to have evidence of increased expression of interleukin 1 messenger RNA and an increase in CD3+ lymphocytes in mucosal biopsy specimens [2,24].

There is a growing body of evidence that inflammation and immune activation contribute to at least a subset of IBS patients. Chadwick et al. showed evidence of immune activation in examined mucosa biopsies from almost 90% of IBS patients who met Rome criteria [24]. Half of these patients had a normal mucosa appearance on routine examination and the remainder had increased cellularity of the mucosa and submucosa with a diagnosis of microscopic colitis. Findings of increased intraepithelial lymphocytes, CD3+ cells, nature killer, and mast cells contribute to the growing body of literature demonstrating an increased inflammatory cell presence in the colonic mucosa of certain IBS patients [2,25]. In patients with PI-IBS, the T cell subgroups remain increased for more than a year after infection. This may reflect immune activation by luminal antigen because of increased intestinal permeability in these patients. Therefore, it is believed that inflammatory stimuli may induce a hyperalgesic state and alter motor function in patients with IBS. The substances that medi-

Table 2. Initial workup in patients suspected of having IBS [10].

Complete medical history
Physical examination
Initial laboratory analyses: complete blood cell count, electrolytes, blood urea nitrogen, creatinine, albumin, C-reactive protein or erythrocyte sedimentation rate
Thyroid-stimulating hormoneLook for alarm symptoms indicating the presence of organic disease
If yes: additional workup; if no: initiate treatment

ate these changes are not fully understood, but there is growing recognition of the role of serotonin as a sensitizing agent [26].

Recent studies have shown that there is interaction between the ENS and the immune system, especially in relation to functional bowel disorders [19]. It was also shown that ENS nerves play a role in gut mucosa integrity and restitution [19]. Thus, alteration in gut immune function may play a role in IBS, but correlation of IBS symptoms with these changes has not been established. Moreover, the majority of patients with gastroenteritis do not develop PI-IBS. It is also interesting that the prevalence of IBS is not higher in countries with high incidences of GI infections. Therefore, further studies are needed to determine which vulnerability factors play a role in the development of PI-IBS. In addition, psychological distress seems to be an important cofactor in determining who retains symptoms after an enteric infection.

The Brain-gut Axis

There is relationship between the function of the CSN and the intestines via the specialized ENS of the gut. The ENS independently controls gut function, the migrating motor complex, and peristalsis, and is constantly monitored and modified by both vagal and sympathetic extrinsic nerves [3].

The brain and gut reciprocally affect the experience and regulation of visceral pain. Visceral signals are transmitted via ascending pathways to the midbrain, thalamus, and cortex. The somatosensory cortex receives somatotypic information about the location and intensity of pain and the limbic system (anterior cingulated cortex, insula, medial thalamus) is involved with the affective and motivational component of pain [27]. The limbic system can modulate the pain experience via activation of descending regulatory pathways [27]. Therefore, normal GI function results from an integration of intestinal motor, sensory, autonomic, and CNS activity, which interact through bidirectional parallel circuits. The BGA links visceral afferent sensations and intestinal motor function with higher cortical centers that modulate and modify their activity.

Neural transmission within the gut (ENS) and brain (CNS) is controlled by numerous neurotransmitters and neuromodulatory peptides, including CRF, vasoactive intestinal peptide (VIP), serotonin and its congeners, calcitonin gene-related polypeptide (CGRP), acetylcholine, substance P, nitric oxide, cholecystokinin, and the enkephalins [18,27,28].

Serotonin (5-HT) is a major neurotransmitter in the GI tract. It plays a key role in the pathogenesis of IBS. In particular, two 5-HT receptors, 5-HT_3 and 5-HT_4, appear to be very important in the control of GI function. They are involved in visceral sensation and in the function of the ENS, including secretion and motility. The gut contains over 95% of the body's 5-HT, and the concentration of 5-HT in the bowel is higher than that in the brain [3]. 5-HT is a signaling molecule which participates in mucosal sensory transduction [3,18]. 5-HT stimulates by varied receptors in the GI tract both vagal and enteric afferent nerve fibers [3]. Before activation of extrinsic afferent nerves, specific stimuli arising within the lumen of the GI tract may activate specialized cells present in the mucosa [18]. The most important are enterochromaffin cells, which act as principal sensory transducers. 5-HT released from these cells acts directly on vagal extrinsic afferent nerves in the mucosa through activation of 5-HT3 receptors exposed on the nerve terminal [18].

As a neurotransmitter in the ENS, 5-HT plays a role in initiating responses as diverse as nausea, vomiting, intestinal secretion, and the peristaltic reflex [3]. Therefore, the antagonism of the 5-HT receptors is useful in the therapy of functional bowel diseases [3].

Diagnosis and Treatment

The diagnosis of IBS is based on the identification of symptoms and the exclusion of organic diseases. The Rome II criteria are usually used in clinical practice to assess the patient's symptoms (Table 1). Physical examination and several initial investigations are needed to exclude organic, metabolic, or infectious diseases (Table 2). A careful search for psychosocial factors, stress, and physical or sexual abuse are also important.

The first and crucial step in the treatment of patients with IBS is establishing an effective and positive physician-patient relationship [1,5,10]. Therapy is based on the dominant symptom (IBS subtype). Therapeutic options include dietary modifications, counseling, medications, and psychological treatments thoroughly described by many authors [1–5,29-35]. Fiber and bulking agents may help constipation, but the evidence that they are efficacious in IBS is equivocal. These agents are frequently prescribed as first-line drugs for IBS regardless of the primary bowel disturbance [30]. Laxatives have no established value in IBS, but are often taken by patients with constipation predominant IBS [5]. Antispasmodics are usually prescribed for abdominal pain [5,29]. Low doses of tricyclic antidepressants may be effective, but side effects and patient concerns regarding use of a centrally acting agent for depression remain limitations [29,30]. Other groups of antidepressants and selective serotonin reuptake inhibitors are of uncertain efficacy in IBS. Loperamide, a mu-opioid agonist, is useful for diarrhea but not for pain in IBS.

Table 3. Drugs useful in the treatment of patients with IBS.

Drug category		Drug name
Antispasmodics		dicyclomine, hyoscyamine, diphenoxylate with atropine (Lomotil), cimetropium, pinaverium, octylonium, trimebutine, mebeverine, peppermint oil
Antidepressants tricyclic		imipramine, amitriptyline, doxepin, desipramine, nortriptyline
Selective serotonin reuptake inhibitors		citalopram, fluoxetine, sertraline, paroxetine
Prokinetic agents		cisapride
Laxatives – bulk-forming		methylcellulose, psyllium
Laxatives – osmotic		magnesium salt, sorbitol, polyethylene glycol, lactulose
Antidiarrheal agents		loperamide, diphenoxylate, cholestyramine
New drugs		
Selective M_3 antimuscarinic agents		zamifenacin, darifenacin
5-HT_3 receptor antagonists		alosetron
5-HT_4 receptor	partial agonists	tegaserod
	full agonist	prucalopride
Cholecystokinin antagonists		loxiglumide
$Alpha_2$-adrenergic agonists		clonidine
Kappa-opioid agonists		fedotozine
Mu-opioid agonist		loperamide
Neurokinin antagonists		ezlopitant, nepadudant

The precise underlying pathophysiology of IBS remains unknown. However, disturbances in the BGA involving the CNS and the ENS have emerged as an underlying concept for IBS [31]. In this regard, the above-mentioned conventional therapy has been recognized as unsatisfactory for many patients with IBS [5,31]. Therefore, novel neuroenteric modulatory compounds have been introduced for clinical use [2,5]. Novel approaches include visceral analgesics, specifically drugs interacting with the 5-HT receptors. Serotonin agonists and antagonists have been demonstrated to be of benefit in some patients in the treatment of IBS. Both reduce visceral sensitivity and change motor activity [2,30]. In patients with severe diarrhea, 5-HT_3 receptor antagonists (alosetron), which retard small bowel and colonic transit and relieve pain, are indicated. However, the indication for alosetron has been restricted and it is used in several countries only for women with severe diarrhea-predominant IBS who have had symptoms for at least 6 months and who have failed to respond to conventional therapy [31]. In patients with constipation, 5-HT_4 agonists (e.g. tegaserod, prucalopride, which accelerate small bowel and colonic transit) are of clinical value. Tegaserod is the first selective 5-HT_4 receptor partial agonist to be approved for the treatment of constipation-predominant IBS. It is active against multiple IBS symptoms; it stimulates gut motility and reduces visceral sensitivity and pain. The drug does not cure IBS and was not designed to treat the diarrhea-predominant version [32]. Tegaserod is available in the United States and other countries for use in women with IBS whose primary bowel symptom is constipation; its efficacy in men and in those with alternating bowel habits has not been established. In patients with IBS and pain, several groups of drugs are helpful, including alfa2-adrenergic agonists (e.g. clonidine, which reduces tone and pain sensation), cholecystokinin antagonists, kappa-opioid agonists (e.g. fedotozine), and neurokinin antagonists (reduce visceral sensation, constipation, bloating), but some of these agents are still being investigated [2,5,33]. In patients with IBS and abdominal pain, several new groups of drugs are obtainable (Table 3) [5,30,31,34,35]. Progress in our understanding of the role of the BGA disturbances is a key to the development of new and effective therapies for IBS [5].

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